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April 27, 2018

The Honorable Claire C. Cecchi
United Stated District Court, District of New Jersey
50 Walnut Street, Courtroom MLK 5B
Newark, NJ 07101

Re: **Defendants' Letter Brief in Support of Proposed Scheduling Order**
In Re: Proton-Pump Inhibitor Products Liability Litigation (No. II)
Case No. 2:17-md-02789-CCC-MF

Dear Judge Cecchi:

Defendants respectfully submit this letter in support of our proposed scheduling order, attached as Exhibit H. In light of recent action by FDA that expressly rejected Plaintiffs' primary theory of liability, Defendants suggest that the Court adopt a schedule that frontloads discovery and motion practice on the threshold issues of general causation and preemption, deferring full generic and case-specific discovery until after the Court decides these issues. If the Court is not inclined to do so, Defendants respectfully request that, at a minimum, the Court rule on dispositive motions on both general causation and preemption before the parties engage in time-consuming, expensive, and potentially wasteful case-specific discovery.

INTRODUCTION

It has been nearly three decades since FDA first approved PPI medications as safe and effective for use in the United States. PPIs were a major advance over the prior standard of care (H2-blockers and antacids), providing far more effective acid suppression and symptom relief. Since their approval, millions of Americans have taken PPIs, and the medications have had a dramatically positive impact on both clinical outcomes and patient quality of life.

In 2016, new observational studies raised questions about a potential association between chronic kidney disease ("CKD") and use of proton pump inhibitor medications ("PPIs"). Thereafter, but before the medical and regulatory communities had an opportunity to weigh in on the reliability of those studies, Plaintiffs' attorneys commenced a sprawling litigation, taking advantage of the natural overlap between a disease that is common in the general population and the large number of people who have taken PPIs at some point in their lives.

It is already apparent that Plaintiffs may have jumped the gun, raising the specter of a large, wasteful and disruptive litigation that has no sound scientific or regulatory basis. Indeed, both the medical and regulatory communities now have had the opportunity to weigh in, finding that the available evidence does not support a causal relationship between PPI use and CKD and that no changes should be made to the warnings provided in the PPI product labels. As a result, this case is different from many pharmaceutical product liability litigations, and a different approach to the sequencing and management of discovery is needed.

First, in 2017, prominent scientific and medical organizations reviewed the very data cited by plaintiffs in their Master Complaint and have determined that, because of significant methodological limitations, the data does not provide reliable evidence of causality. This conclusion is reflected in published statements of leading organizations such as the American Gastroenterological Association ("AGA") and the National Kidney Foundation. Indeed, no reputable organization in the field has concluded that PPI medications cause CKD.

Second, beginning in 2016, FDA conducted a formal review of the kidney safety of PPI medications and the adequacy of the relevant information included in the product labeling. That review, which included detailed analysis of the studies at issue here, concluded that significant potential sources of bias existed in the studies, the "evidence for causal association [was] too weak to offset [the] severe risk of bias," and "biological explanations [for an association with CKD] seem speculative at this time." Based on these findings, by late 2017, FDA determined that no changes should be made to the warnings provided in the product labeling for PPI medications and publicly announced its conclusions.

While the litigation ship has sailed, these developments raise significant questions regarding Plaintiffs' ability to provide reliable expert evidence and data to establish general causation. Defendants also believe that there are strong bases for a preemption defense, including FDA's regulatory determination which makes clear that Defendants could not independently have made any relevant changes to the existing warnings in PPI labeling.[1]

Accordingly, and against this unique backdrop, Defendants respectfully request the Court set a schedule that requires the parties to undertake limited discovery, to conduct *Daubert* hearings, and to brief summary judgment motions on the threshold issues of general causation and preemption before engaging in time-consuming, expensive, and disruptive full discovery of Defendants and individual Plaintiffs.[2] Early resolution of these threshold issues will advance the ultimate objective of the MDL process: addressing issues common to all Plaintiffs and providing valuable information that will help the Court and parties evaluate and resolve this litigation as efficiently as possible. Moreover, PSC's recent shotgun filings of thousands of lawsuits that name every conceivable PPI product and claim a wide array of kidney injuries, as well as the PSC's request to toll thousands of additional cases to allow time to identify proper defendants and injuries, make clear that most of these cases are not ready for case-specific adjudication, and thus no prejudice will come to Plaintiffs if the Court adopts Defendants' proposed schedule.

BACKGROUND

Observational Studies: Questions about CKD Risk with PPIs. None of the hundreds of clinical trials conducted over the last three decades have reported an association between PPI use and CKD. However, starting in 2016, certain observational studies raised questions about a

[1] Defendants also believe that Plaintiffs' design defect claims are preempted under the rationale in *Yates v. Ortho–McNeil–Janssen Pharm., Inc.*, 808 F.3d 281, 298 (6th Cir. 2015).

[2] Production of Plaintiff Fact Sheets ("PFS") and proof of use and injury records should occur simultaneously with the bifurcated approach Defendants are suggesting so as to allow the parties and the Court to determine which Defendants, if any, are properly in each case and to winnow the Plaintiff pool as appropriate.

potential risk. As the Court will hear at Science Day, those studies have significant methodologic limitations, which preclude them (either individually or as a group) from providing reliable evidence of causation. Indeed, the study authors themselves emphasize the inherent limitations of their studies and acknowledge that they do not establish causality. For example, the authors of the Lazarus 2016 study (the first and most widely cited study on this topic) note numerous limitations of their analysis and expressly state that the study "does not provide evidence of causality." (*See* Ex. A at 244-45.) Likewise, the authors of a recent meta-analysis evaluating the safety of PPIs concluded that the strength of the evidence linking PPI use and CKD was "low" and that causality "cannot be established." (*See* Ex. B at 8-9.)

Medical and Scientific Organizations: Evidence Is Low Quality and Insufficient for Causality. In 2017, the AGA—the preeminent U.S. medical association of gastroenterologists—published a review of the data on PPI use and CKD. AGA found that the overall quality of the evidence was "very low" and that, while "thought-provoking," the available studies have "inherent limitations" that preclude them from supporting causality. (*See* Ex. C at 707, 709 Table 1.) Based on this review, AGA recommended *against* routine monitoring of kidney function in patients treated with PPIs. (*See id.* at 706-07.) Likewise, the National Kidney Foundation (the leading organization in the U.S. dedicated to the awareness, prevention and treatment of kidney disease) has stated that, "[while] some studies suggest there is an increased risk of chronic kidney disease," "[i]t has not been proven that PPI use causes chronic kidney disease." (*See* Ex. D at 2.) Defendants are not aware of any reputable medical or scientific organization that has concluded otherwise.

FDA: Data Insufficient to Establish Causality / No Basis for Regulatory Action. In 2016, FDA's Office of Surveillance and Epidemiology ("OSE") reviewed the data purportedly linking PPI use with CKD, focusing on two of the key studies referenced by plaintiffs (Lazarus 2016 and Xie 2016). With regard to Lazarus, FDA identified problems with potential "confounding and outcome misclassification" and concluded that the data "does not permit a confident conclusion that identifies PPIs as a cause for CKD." (*See* Ex. E at FDA-00000027, FDA-00000037, FDA-00000041.) As to Xie 2016, FDA determined that the study findings are "subject to severe risk of bias," "evidence for causal association [was] too weak to offset [the] severe risk of bias," and "biological explanations [for an association with CKD] seem speculative at this time." (*See id.* at FDA-00000004, FDA-00000015-17.)

These OSE reviews coincided with FDA opening a Tracked Safety Issue ("TSI") for PPIs and CKD. FDA opens a TSI when FDA staff identify a potential signal of a serious risk with a medication, and FDA can take any corrective action necessary, including requiring labeling changes or withdrawing the medication. (*See* Ex. F at 1-3.) In October 2017, FDA completed its review and concluded that "no action is necessary at this time based on available information." In particular, the Agency did not request any changes to the PPI labeling. (*See* Ex. G at 6.)

In sum, the scientific, medical and regulatory communities reviewed the very studies Plaintiffs rely on and concluded that they do not establish causality and do not support any relevant changes to the PPI labeling. Given this, serious questions exist about Plaintiffs' ability to put forth reliable evidence establishing general causation. Further, based on FDA's regulatory determination, Defendants believe that plaintiffs' claims are preempted by federal law.

ARGUMENT

The Court Should Address General Causation and Preemption First. The *Manual for Complex Litigation* advises that, in complex proceedings like this one, courts "should tailor case-management procedures to the needs of the particular litigation and to the resources available from the parties and the judicial system." Federal Judicial Center, *Manual for Complex Litigation (Fourth)* § 10.1, at 8 (2004). The *Manual* also explicitly advises courts to "take[] up early" the issue of general causation, *id.* § 22.634, at 411, noting that general causation is a "pivotal" issue that may "provide the foundation for a dispositive motion," *id.* § 11.422, at 54–55. Following this recommendation, numerous MDL courts—including the court which oversaw the Nexium/fracture litigation—have structured discovery to focus initially on general causation.[3]

This litigation presents the quintessential case for early consideration of general causation. Recent scientific and regulatory evaluations consistently have found no sound scientific basis on which to conclude that there is a causal link between PPIs and CKD. Given that, addressing general causation at the outset has the potential of saving significant time and resources and may "preempt[] the need for almost all of the discovery" that otherwise would be undertaken. *In re Agent Orange Prod. Liab. Litig.*, 506 F. Supp. 762, 767-68 (E.D.N.Y. 1980). While such an approach defers certain case-specific discovery, it does not alter the burden that Plaintiffs undertook when they commenced this litigation—to provide reliable expert evidence and data to establish that PPI medications are capable of causing CKD. Moreover, considering the PSC's request for tolling and tacit acknowledgment that the lion's share of their cases are not yet ripe for case-specific discovery, presumably any interruption would (at most) only impact a small percentage of the plaintiffs.

Similarly, the potential that Plaintiffs' claims are preempted—for the prescription PPIs, over-the-counter PPIs, or both—also warrants early consideration by the Court. If the Court finds that FDA would not have permitted Defendants to independently make changes to the warnings provided with—and/or the design of—PPIs, Plaintiffs' state law claims would be subject to dismissal pursuant to the U.S. Supreme Court's holding in *Wyeth v. Levine*, 555 U.S. 555 (2009). Further, much of the discovery that would be relevant to general causation also would be relevant to preemption, making it relatively straightforward for the Court and parties to sequence the discovery in a way that focuses the litigation on potentially dispositive issues. Attached as Exhibit H is a proposed schedule that would implement this frontloaded approach. Under this schedule, *Daubert* hearings would take place in the fall of 2019.

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[3] *See, e.g.*, *In re Nexium Esomeprazole*, 662 F. App'x 528, 530 (9th Cir. 2016) (memorandum disposition); *In re Zoloft Prods. Liab. Litig.*, 858 F.3d 787, 800 (3d Cir. 2017); *In re Mirena IUD Prod. Liab. Litig.*, No. 16-2890, 2017 WL 4785947, at *3 (2d Cir. Oct. 24, 2017) (per curiam), *petition for cert. docketed*, No. 17-1037 (Jan. 22, 2018); *In re: Incretin-Based Therapies Prods. Liab. Litig.*, MDL No. 2452, Dkt. 2401 (S.D. Cal. Mar. 21, 2018); *In re: Incretin-Based Therapies Prods. Liab. Litig.*, MDL No. 2452, Dkt. 325 (S.D. Cal. Feb. 18, 2014); *In re Bextra & Celebrex Liab. Litig.*, MDL No. 1699, Dkt. 178, at 1-4 (N.D. Cal. Mar. 16, 2007); *In re Viagra Prods. Liab. Litig.*, MDL No. 1724, Dkt. 38, at 1 (D. Minn. June 30, 2006); *In re Phenylpropanolamine (PPA) Prods. Liab. Litig.*, MDL No. 1407, Dkt. 340, at 1 (W.D. Wash. Mar. 22, 2002).

Frontloading general causation and preemption will save the parties from conducting potentially dozens of depositions and producing millions of pages of documents about issues that are not relevant to those potentially dispositive defenses, including Defendants' marketing of PPIs. In the alternative, if the Court does not frontload general causation and preemption, it should at a minimum consider dispositive motions on those issues immediately after Plaintiffs complete all generally applicable discovery.[4] (*See* Ex. H at ¶¶ 1(b) & n.1, 2 [allowing additional time for marketing and other discovery without delaying dispositive motions].)

The Court Should Defer the Selection of, and Discovery in, Individual Cases for Early Trials. While common discovery is taking place (whether limited to general causation and preemption or not), the Court should not require the parties to conduct case-specific discovery beyond the production of PFS's, pharmacy records, and medical records. During recent discussions with the Court regarding bundling of complaints and tolling agreements, Plaintiffs' counsel advised the Court that they will need a substantial amount of time to identify which PPIs each Plaintiff used. As a result, the contours of the docket—including which Defendants belong in which cases—will not be clear for some time. Rather than rush to select cases that may not be representative of the docket as a whole, the Court should wait until it becomes clear which Plaintiffs can establish that they: (1) used certain PPIs, including which PPIs those Plaintiffs used; and (2) suffered a kidney injury following that use, as documented in medical records. Further, the Court's rulings on the dispositive motions will put the parties in the best position to decide which cases, if any, are appropriate for additional case-specific discovery (presumably, only those where plaintiffs have established use of a PPI and a kidney injury that followed PPI use). Until the docket becomes clearer, it is impossible for the Court and the litigants to select cases that will provide meaningful information to the parties.

Defendants' proposed schedule will not unduly delay case-specific discovery. While the parties complete production of PFS's and records, conduct common discovery, and brief dispositive motions, they can meet and confer to identify a process for selecting cases for early discovery and prepare a case management order governing further discovery in those cases, if needed. Those steps will ensure that, in the event the Court denies Defendants' motions, the parties are ready to move quickly to prepare cases for trial.

CONCLUSION

Accordingly, Defendants respectfully request that the Court adopt a scheduling order that limits the initial phase of discovery to the issues of general causation and preemption, with briefing and hearings on *Daubert* and summary judgment motions to follow immediately thereafter. If the Court declines to do so, Defendants request that, at a minimum, the Court provide for briefing and hearings on these threshold issues before the parties engage in expensive, time-consuming, and potentially unnecessary case-specific discovery.

[4] In conjunction with entering a schedule for discovery that is generally applicable to Defendants, Defendants also request that the Court establish reasonable limits on the volume of discovery Plaintiffs may conduct, including the number of custodial files and depositions Plaintiffs may take. Defendants are submitting a separate brief in support of their proposed case management order regarding discovery limits.

Dated: April 27, 2018

Respectfully submitted,

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